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(54) A STRUCTURE HAVING A MICROCRYSTALLINE COLLAGEN LAYER AND METHOD OF PREPARING THE SAME

(71) We, AVICON, INC., of Fort Worth, in the State of Texas, United States of America, a corporation organized and existing under and by virtue of the laws of the State of Delaware, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns a structure having a microcrystalline collagen surface layer and a method of preparing the same.

Various techniques are known for the preparation of structures containing flocked finely divided materials, and numerous materials have been employed in the preparation and deposition of flocked structures and coatings.

For example, it is known to deposit by electrostatic deposition various materials on to a suitable carrier, see for example, U.S. Patents Nos. 2,551,035, 2,592,602, 3,194,702, 3,202,539, 3,323,933, 3,457,080 and 3,492,144.

It is an object of this invention to provide an improved structure comprising microcrystalline collagen, and processes of preparing the same, said structures being useful as bandages, surgical dressings, special papers, sponges, haemostatic pads and mats.

In accordance with one aspect of the invention, there is provided a structure comprising a substrate having a layer consisting esesntially of microcrystalline collagen deposited on said substrate by electrostatically attracting microcrystalline collagen particles on to said substrate.

Viewed from another aspect, the invention provides a structure comprising a supporting substrate and a surface layer of finely divided, flocked, microcrystalline collagen particles, at least 1% by weight being particles whose maximum dimension in any one direction is less than 1 micron, and such particles having one end secured to the substrate as a result of electrostatic attraction of the particles to the substrate.

The invention also covers a method of producing the said microcrystalline collagen structure, such method comprising electrostatically depositing the divided microcrystalline collagen particles on to the substrate.

Thus, for example, the said method may comprise moving the substrate past a coating station, supplying the microcrystalline collagen particles to the said coating station, electrostatically charging the said microcrystalline collagen particles so that the resulting charged microcrystalline collagen particles are attracted on to a surface of the said substrate moving past said coating station to effect deposition of the said microcrystalline collagen particles on to said substrate, and removing from said coating station the resulting treated substrate now provided with a coating of the microcrystalline collagen particles on a surface thereof.

Microcrystalline collagen is a collagen material commercially available under the trade name AVITENE, manufactured and/or sold by FMC Corporation, of Princeton, New Jersey, U.S.A.. The preparation and properties of microcrystalline collagen are disclosed in our British Patents Nos. 1,156,361, 1,224,925 and 1,144,552.

Solid, finely divided microcrystalline collagen is a form of collagen in a physical state intermediate that of swollen fibrils and tropocollagen. This physical form of collagen is microcrystalline and colloidal and it consists of bundles of aggregated tropocollagen units which vary in length from that of an individual tropocollagen unit (about 25 to 50 Angstrom Units) to just under one micron and a diameter from about 25 Angstrom Units to some hundreds of Angstrom Units. Compositions comprising various forms of collagen, at least 10% by weight of which comprise the microcrystalline collagen employed in the practices of this invention and which are substantially free of tropocollagen and degraded derivatives thereof, produce

[*Price 25p*]

viscosity-stable aqueous gels at low concentrations, for example 1%.

The microcrystalline collagen employed in the practices of this invention should preferably contain at least 1% by weight of submicron colloidal particles, that is, particles whose maximum dimensions in any one direction is less than 1 micron. The said particles are of fibril-like form. The microcrystalline collagen is unique in its characteristics of forming aqueous soliquoid or non-elastic type gel in concentrations of 0.5% dispersed salt, the gel exhibiting a pH of about 3.2 ± 0.2 and having a substantially stable viscosity for at least 100 hours at 5°C. when stored in a closed container. This is in sharp contrast to the aqueous elastic or emulsoid type gels formed by tropocollagen and degraded forms of collagen, such as gelatin, which thicken or exhibit substantial increases in viscosity on standing to produce rubbery mixes.

As disclosed in the aforementioned patents, the finely divided microcrystalline collagen employed is prepared from any native collagen in the natural state, either as pieces or as original hide or gut, but preferably as pieces dried under non-denaturing conditions and chopped up for easier handling. The undenatured collagen is treated under carefully controlled conditions with very dilute acid, the pH of which is in the range from 1.6 to 2.7, conveniently between 1.7 and 2.6. When the collagen-containing material is wet, the proportion of water present should be taken into consideration in the preparation of the acid solution to be used in the treatment of the collagen-containing material. The material is then mechanically disintegrated in the presence of the dilute acid until at least 1%, preferably 25 to 85% or more, of the collagen-containing material is reduced to a submicron size. It is not essential that all of the collagen-containing material is reduced to submicron size since the resulting product is useful when only about 10% or less has been so reduced, although optimum results are obtained substantially at higher concentrations of the submicron material.

For making microcrystalline colloidal collagen, thorough soaking of the hide or collagen-containing material with the appropriate dilute acid at the required pH is necessary.

When employed hydrochloric acid as the acid treating agent and when employing vacuum freeze-dried cowhide as the collagen source material, it is essential that the pH of the treating solution not exceed about 2.7 to produce the microcrystalline colloidal collagen upon subsequent disintegration. Optimum results at a concentration of 1% solids are obtained with acid solutions having a pH of the order of 2. Treatment with solutions having a pH of less than 1.6 tends to cause rapid degradation of molecular weight with an attendant build-up of acid soluble tropocollagen and other degradation products, as evidenced by a marked drop in apparent viscosity.

The action of the acid treatment is threefold. First, the acid serves to cause limited swelling of the fibres. Second, there is a limited hydrolysis of seletcive peptide linkages within the non-crystalline or amorphous regions of the collagen fibrils so that subsequent mechanical disintegration permits a ready fragmentation of the weakened morphology into microcrystalline particles having dimensions between those of tropocollagen and collagen fibrils. Third, a portion of the acid reacts with free primary amino groups of the collagen to form what may be termed collagen hydrochloride salt which, of course, is ionized in the presence of water.

After the acid treatment, the hide substance, with the acid homogeneously distributed therethrough, is subjected to mechanical attrition to reduce a portion thereof, e.g. at least ten percent, to submicron size. The preferred disintegrating equipment, such as a "Waring Blendor" or a "Cowles Dissolver" for low solids concentration, subjects the particles of treated collagen to high shear against each other, causing disruption and effective reduction in size of the subfibril microcrystalline aggregates. High shear can be imparted in other ways, as by extrusion through small orifices as by the use of a "Bauer Refiner" ('Bauer' is a registered trade mark) and "Rietz Extructor", particularly as in the case of high (about 5%) solids concentrations, and by other known techniques. Preferably, the disintegration is continued well beyond the point where ten percent of the product is submicron in size, e.g. until fifteen to twenty percent or even much more of this product has been reduced to colloidal size.

Hydrochloric acid is employed as the acid treating agent merely because it is relatively inexpensive and allows ready flexibility and ease of control. Other acids, both inorganic and ionizable organic acids, are useful, such as sulfuric acid, hydrobromic acid, phosphoric acid, cyanoacetic acid, acetic acid and citric acid. Sulphuric acid, for example, is satisfactory, but control of its action is difficult. Citric acid may be substituted for hydrochloric acid, hydrobromic acid, phosphoric acid, cyanoacetic acid, with reference to its ability to arrest the swelling and hydrolysis of the collagen fibres at that point whereby the insoluble colloidal material is formed and is retained while preventing the rapid degradation of the material to a soluble product.

Upon completion of the disintegration, the gels produced have a pH of from 2.6 to 3.8,

the specific pH being dependent upon the pH of the treating acid. Preferably, the pH of the gels exhibiting optimum properties is between 3.0 and 3.3. For example, in the preparation of 1% by weight gel, one part of finely ground, vacuum freeze-dried cowhide was treated with 100 parts by weight of a hydrochloric acid solution, having a pH of 2.25. After a 15 minute treatment in a "Waring Blendor", the gel had a pH of 3.25. A 2% by weight gel was prepared in like manner and had a pH of 3.3. When 1 gram samples of finely divided microcrystalline collagen were prepared by drying these gels and the samples placed in 100 mls. of distilled water the partial hydrochloride salt of collagen ionized and the pH of water was lowered to a pH of 3.1.

The microcrystalline material exhibits high water absorption properties and products made from this material do not tend to disintegrate in water. Accordingly, the finely divided microcrystalline collagen is useful for the preparation of materials and structures useful as wound dressings and in surgical procedures.

For some uses it is desirable to remove the free fatty material which may be present in the fiinely divided microcrystalline collagen. This removal may be effected by adding cellulosic fibres in the form of highly bleached kraft wood pulp or microcrystalline collagen with appropriate mixing to distribute uniformly the cellulosic material throughout the resulting dispersion. Subsequent filtration of the resulting dispersion, such as by conventional pressure filtration, results in a significant removal of the natural fatty materials originally present in the collagen source material. Alternative procedures to reduce such fatty materials to minimal levels are the extraction of the raw undried hides or collagen source material with organic solvents, suc has acetone, which will dissolve the fatty materials, or to force the dispersions through cellulose paper or fabric filters under very high pressures. Such filtration steps furthermore help to remove extraneous small amounts of other impurities, such as chips of hair and fleshy tissues, which are usually undesirable in the finished microcrystalline collagen-containing products.

If desired, the wet strength of the microcrystalline collagen-containing materials used in the structures prepared in accordance with this invention may be improved by incorporating cross-linking agents in the manufacturing process, particularly at the beginning of the attrition stage for the production of the microcrystalline collagen. Typical cross-linking agents which are satisfactory include the various formaldehyde-base cross-linking agents, such as, for example, urea-formaldehyde precondensate and malamine-formaldehyde precondensate, glyoxal acetaldehyde, potassium alum, chrome alum, iron alum, basic aluminium acetate, cadmium acetate, copper acetate, barium hydroxide, water-soluble diisocyanates. The specific cross-linking agent which is utilized depends upon the desired end use of the microcrystalline collagen-containing product. The cross-linking agents serve to improve the wet strength of the finished products. An additional benefit is provided by the use of certain of the cross-linking agents, viz. an improvement in the heat resistance of the final product.

The said substrate may, for example, be rough and porous so that, as the said electrostatically charged microcrystalline collagen particles are attracted to and deposited on the said surface, the resulting deposited microcrystalline collagen particles penetrate and are firmly attached to the said surface.

If desired the substrate may be perforated.

For certain applications, the substrate may comprise a felted, knitted or woven fibrous material.

In one example of the method of the invention, the said substrate, prior to the eletcrostatic deposition of the microcrystalline collagen particles thereon, has or is provided with an adhesive coating on the said surface for adhesively securing the microcrystalline collagen particles on to said surface when the said microcrystalline collagen particles are electrostatically deposited on said surface.

The said substrate may comprise a film consisting of or carrying an adhesive coating. Such a film may, for instance, comprise collagen, for example, an aqueous microcrystalline collagen gel.

In a further example, the said film may comprise a synthetic plastics film and the said plastics film is provided with a coating of an aqueous microcrystalline collagen gel, the said coating providing the surface upon which the said microcrystalline collagen particles are to be deposited.

According to another feature of the method of the invention, the said adhesive coating may contain a volatilizable liquid solvent, and the said solvent may be evaporatively removed from said adhesive coating subsequent to the deposition of the said microcrystalline collagen particles, for example by irradiating the adhesive and microcrystalline coated surface with infra-red radiation.

Structures in accordance with this invention are useful wherever absorbent material may be desired, e.g. disposable diapers, sanitary napkins, swabs, surgical sponges, industrial and domestic sponges, pads, applicators, tampons, surgical dressings, or cigarette filters. By way of example, when the structures of this invention are to be used as

haemostatic pads or bandages, the microcrystalline collagen coating is usually applied to the substrate in an amount in the range 1—30 mg/cm², usually an amount in the range from 2 to 20 mg/cm².

There may also be incorporated in the structures prepared in accordance with this invention a pharmaceutical or a medicinal compound or agent. Such an agent may be incorporated during the process for the preparation of the microcrystalline collagen or in admixture with the microcrystalline collagen in the manufacturing operation involving electrodeposition of the finely divided microcrystalline collagen for the preparation of structures in accordance with this invention. If desired, also, such agents may be incorporated in the finely divided microcrystalline collagen-containing structures prepared in accordance with this invention subsequent to the electrodeposition of the microcrystalline collagen.

Referring now to the drawing, which schematically illustrates the preparation of of structure prepared in accordance with this invention, a finely divided microcrystalline collagen is contained within hopper 11 which is positioned over a suitable substrate 12 which is moved on and by rollers 14 and 15. Substrate 12 may comprise a film of material, such as a cellulosic film, which may be coated with an aqueous collagen-containing gel as adhesive material, and passes beneath bottom outlet 11*a* of hopper 11. Finely divided microcrystaline collagen which has received an electrostatic charge by means of generator 16 falls through bottom outlet 11a of hopper 11 upon travelling substrate 12 which is also appropriately but oppositely electrostatically charged by generator 16.

As the finely divided microcrystalline collagen falls through outlet 11*a* of hopper 11, it is attracted to the oppositely charged surface of substrate 12 and forms a uniform adherent coating or layer of finely divided microcrystalline collagen thereon. If desired, as illustrated, dryer 18 may be provided so as to dry or cure any adhesive material which might be present on the surface of the substrate so as to better secure the electrostatically deposited layer of finely divided microcrystalline collagen thereto. After passage through dryer 18, the substrate coated with finely divided microcrystalline collagen passes over roller 15 and is directed, as indicated, to a suitable product take-up roller.

The electrodeposition of finely divided microcrystalline collagen onto a suitably charged substrate is particularly satisfactory.

A uniform coating of microcrystalline collagen can thereby be deposited on the substrate. This uniform coating of microcrystalline collagen can be deposited on the substrate since the surface of the substrate can be given a substantially uniform charge of a polarity opposite that of the charged finely divided microcrystalline collagen as it leaves outlet 11*a* of hopper 11. By employing electrostatic deposition, it is possible to deposit a layer of finely divided microcrystalline collagen onto all the exposed surfaces of the substrate, including the surfaces of crevices and the interstices, ordinarily difficult to reach surfaces. Further, the resulting electrostatically deposited layer of finely divided microcrystalline collagen is substantially uniform in appearance.

In practice, the finely divided particles or fibrils microcrystalline collagen would tend to be attracted to the oppositely charged substrate such that an end of the finely divided microcrystalline collagen fibrils would first contact the substrate and tend to adhere thereto, particularly in the tance where the substrate is provided wit. .n adhesive material. Under such conditions, the resulting electrostatically deposited fibrils would tend to be deposited on-end onto the substrate, with the resulting production of an improved coating of finely divided microcrystalline collagen. From a physical point of view such a coating would not appear to be otherwise obtainable than by electrostatic deposition in accordance with this invention.

Although the practice of this invention has been schematically illustrated in the drawing as being directed to the electrostatic deposition of a coating of microcrystalline collagen on to a substrate, complicated multi-layer structures containing electrodeposited microcrystalline collagen can be prepared by employing the practices of this invention.

WHAT WE CLAIM IS:—

1. A structure comprising a substrate having a layer consisting essentially of microcrystalline collagen deposited on said substrate by electrostatically attracting microcrystalline collagen particles on to said substrate.

2. A structure comprising a supporting substrate and a surface layer of finely divided, flocked, microcrystalline collagen particles, at least 1% by weight being particles whose maximum dimension in any one direction is less than 1 micron, and such particles having one end secured to the substrate as a result of electrostatic attraction of the particles to the substrate.

3. A structure according to claim 1 or 2, wherein the amount of microcrystalline collagen particles is from 1 to 30mg./sq.cm of the substrate area.

4. A structure according to claim 1, 2 or 3, wherein the microcrystalline collagen particles are secured to the substrate by an adhesive.

5. A structure according to any one of claims 1 to 4, wherein the substrate is a felted, knitted or woven fibrous material.

6. A structure according to any one claims 1 to 4, wherein the substrate is a cellulosic film.

7. A structure according to any one of the preceding claims, wherein a pharmaceutical compound is admixed with the microcrystalline collagen particles.

8. A method of producing the structure of claim 1 or 2, comprising electrostatically depositing the divided microcrystalline collagen particles on to the substrate.

9. A method according to claim 8 and comprising moving the substrate past a coating station, supplying the microcrystalline collagen particles to the said coating station, electrostatically charging the said microcrystalline collagen particles so that the resulting charged microcrystalline collagen particles are attracted on to a surface of the said substrate moving past said coating station to effect deposition of the said microcrystalline collagen particles on to said substrate, and removing from said coating station the resulting treated substrate now provided with a coating of the microcrystalline collagen particles on a surface thereof.

10. A method according to claim 9, wherein the said substrate, prior to the electrostatic deposition of the microcrystalline collagen particles thereon, has or is provided with an adhesive coating on the said surface for adhesively securing the microcrystalline collagen particles on to said surface when the said microcrystalline collagen particles are electrostatically deposited on said surface.

11. A method in accordance with claim 9, wherein the said substrate comprises a film consisting of or carrying an adhesive coating.

12. A method according to claim 11, wherein the said film comprises collagen.

13. A method according to claim 12, wherein the said film comprises an aqueous microcrystalline collagen gel.

14. A method according to claim 13, wherein the said film comprises a synthetic plastics film and the said plastics film is provided with a coating of an aqueous microcrystalline collagen gel, the said coating providing the surface upon which the said microcrystalline collagen particles are to be deposited.

15. A method according to claim 10 or 11 or any claims dependent on claim 10 or 11, wherein the said adhesive coating contains a volatilizable liquid solvent, and the said solvent is evaporatively removed from said adhesive coating subsequent to the deposition of the said microcrystalline collagen particles.

16. A method according to claim 15, wherein the said volatilizable liquid solvent is evaporatively removed by irradiating the adhesive and microcrystalline coated surface with infra-red radiation.

17. A method according to claim 7 or 8, wherein the said surface of the substrate is rough and porous so that, as the said electrostatically charged microcrystalline collagen particles are attracted to and deposited on the said surface, the resulting deposited microcrystalline collagen particles penetrate and are firmly attached to the said surface.

18. A method according to any one of claims 8 to 17, wherein the said substrate comprises a felted, knitted or woven fibrous material.

19. A method according to any one of claims 8 to 18, wherein the said substrate is perforated.

20. A method of producing a structure in accordance with claim 1, substantially as hereinbefore described.

21. A structure whenever produced by the method of any one of claims 8 to 20.

22. A structure, e.g. a bandage, pad, mat and surgical dressing, having haemostatic properties and incorporating a structure according to any one of claims 1 to 7 and 21.

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1 SHEET *This drawing is a reproduction of the Original on a reduced scale*